Acute Kidney Injury Associated with Late-Onset Neonatal Sepsis: A Matched Cohort Study

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Objectives To determine incidence and severity of acute kidney injury (AKI) within 7 days of sepsis evaluation and to assess AKI duration and the association between AKI and 30-day mortality.

Study design Retrospective, matched cohort study in a single-center level IV neonatal intensive care unit. Eligible infants underwent sepsis evaluations at ≥72 hours of age during calendar years 2013-2018. Exposed infants (cases) were those with culture-proven sepsis and antimicrobial duration ≥5 days. Nonexposed infants (controls) were matched 1:1 to exposed infants based on gestational and corrected gestational age, and had negative sepsis evaluations with antibiotic durations <48 hours. AKI was defined by modified neonatal Kidney Disease Improving Global Outcomes criteria. Statistical analysis included Mann-Whitney and χ^2 tests, multivariable logistic regression, and Kaplan-Meier time-to-event analysis.

Results Among 203 episodes of late-onset sepsis, 40 (20%) developed AKI within 7 days after evaluation, and among 193 episodes with negative cultures, 16 (8%) resulted in AKI ($P = .001$). Episodes of sepsis also led to greater AKI severity, compared with nonseptic episodes ($P = .007$). The timing of AKI onset and AKI duration did not differ between groups. Sepsis was associated with increased odds of developing AKI (aOR, 3.0; 95% CI, 1.5-6.2; $P = .002$). AKI was associated with increased 30-day mortality (aOR, 4.5; 95% CI, 1.3-15.6; $P = .017$).

Conclusions Infants with late-onset sepsis had increased odds of AKI and greater AKI severity within 7 days of sepsis evaluation, compared with age-matched infants without sepsis. AKI was independently associated with increased 30-day mortality. Strategies to mitigate AKI in critically ill neonates with sepsis may improve outcomes. *(J Pediatr 2021;231:185-92)*.

Late-onset sepsis is a significant cause of morbidity and mortality in the neonatal intensive care unit (NICU), with incidence ranging between 10% and 41% depending on infant birthweight.[1,2] The relationship between sepsis, organ injury, and death is well-described in the pediatric intensive care unit, but less is known in the neonatal population, including renal outcomes in patients with sepsis.[3-5]

Lack of consensus definitions for neonatal organ dysfunction were a barrier to prior research, but the 2013 neonatal Kidney Disease Improving Global Outcomes (nKDIGO) guidelines established a foundation for studying neonatal acute kidney injury (AKI).[6-8] Critically ill infants are at unique physiologic risk for AKI, owing to renal immaturity and postnatal fluctuations in renal blood flow.[8] A large international study observed a 30% prevalence of AKI among NICU patients, which was associated with longer hospitalizations and higher mortality.[9]

AKI has been associated with numerous comorbidities of prematurity, including congenital heart disease, necrotizing enterocolitis (NEC), chronic lung disease, and intraventricular hemorrhage, among others.[10-17] Neonatal sepsis may compound the risk for AKI, owing to the contributions of altered hemodynamics, inflammation, and nephrotoxic medications.[18-21] We previously identified an 8% incidence of new renal dysfunction among a cohort of 77 infants with culture-proven sepsis, and another study of 679 infants with fatal sepsis described a 40% incidence of renal dysfunction.[22,23] A better understanding of the risk factors for sepsis-associated AKI, and the pattern of disease severity and duration, may inform clinical approaches to AKI surveillance, risk mitigation, and prognostication.

The primary aim of this study was to determine the incidence and severity of late-onset sepsis-associated AKI occurring within 7 days after sepsis evaluation. Secondary objectives included an assessment of the timing of AKI onset and

AKI	Acute kidney injury
ECMO	Extracorporeal membrane oxygenation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
nKDIGO	Neonatal Kidney Disease Improving Global Outcomes

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duration, and of the relationship between late-onset sepsis, AKI, and mortality within 30 days after sepsis evaluation.

Methods

We performed a matched retrospective cohort study of infants admitted to the Children's Hospital of Philadelphia level IV NICU who underwent sepsis evaluations after 72 hours of life. This 102-bed NICU cares for a mix of outborn infants transferred for subspecialty referral care and inborn infants with prenatally diagnosed congenital anomalies. We used a matching strategy for the following reasons: to decrease confounding owing to the heterogenous nature of infants in the NICU, and to limit misclassification of nonsystemic etiologies of infections (eg, viral, local sources) (**Figure 1**; available at www.jpeds.com). The study period encompassed January 1, 2013, to December 31, 2018; all sepsis evaluations occurring during this time were eligible for inclusion. Patients requiring dialysis during the study period were transferred to the pediatric intensive care unit. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board and granted a waiver of informed consent.

Participants

Sepsis cases were defined as all infants who underwent sepsis evaluations (identified by concurrent blood culture and parenteral antibiotic orders) with subsequent culture-proven bacteremia, fungemia, or meningitis, and who received 5 or more days of systemic antimicrobial therapy (or death before completion of the antibiotic course). The initial antibiotic regimen for suspected late-onset sepsis was vancomycin and cefepime, which was continued either until positive cultures were speciated (and antibiotics narrowed), or discontinued at 48 hours if cultures remained negative. Vancomycin was dosed by our institutional protocol at 15 mg/kg/dose, with the dosing interval dependent on postnatal age and weight. Vancomycin troughs are not routinely obtained unless treatment duration exceeds 48 hours or renal dysfunction is present. The inclusion of multiple sepsis episodes from an individual patient required the following: (1) at least 14 days elapsed between sepsis evaluations, suggesting onset of a new infectious episode, and (2) cultures demonstrated growth of a new pathogen. Infants with coagulase-negative staphylococcal bacteremia were included as cases (even if only 1 positive blood culture) if they otherwise fulfilled the inclusion criteria.

Nonexposed infants ("controls") underwent sepsis evaluations and subsequently had negative blood cultures and an antibiotic duration of less than 48 hours. These infants had no positive bacterial, fungal, or viral testing from any source concurrent with their sepsis evaluation. There was no patient crossover between groups; no patient included as a case had a negative sepsis evaluation included in the control cohort, and vice versa. The pool of potential controls included all qualifying negative sepsis evaluations during the study period. Each sepsis case was matched 1:1 by gestational age and corrected gestational age to the closest control evaluation episode. We excluded infants less than 72 hours of age (to exclude cases of early-onset sepsis) and sepsis evaluations initiated outside the NICU or within 48 hours of admission. We did not include episodes of culture-negative sepsis in this study owing to the heterogeneity in disease processes and outcomes in this subgroup.

Data Collection

Data were extracted from our institutional NICU sepsis registry, which contains electronic health record-linked clinical data encompassing all sepsis evaluations occurring in our NICU. Upon establishing the case and control cohorts, we extracted data encompassing patient demographics, laboratory data, vasopressor and respiratory support, and mortality. Vasopressor support was defined as any daily documented infusion of dopamine (≥4 μg/kg/min, to exclude patients on low-dose infusions for pulmonary hypertension or related indications), or epinephrine, norepinephrine, or dobutamine at any dose. Ventilator support was defined as any documented daily use of invasive conventional or high-frequency mechanical ventilation. For analyses with AKI as the outcome, we counted ventilator and vasopressor days within the 7 days before and after sepsis evaluation (a 14-day period); for analyses with 30-day mortality as the outcome, we counted ventilator and vasopressor days in the 30 days after sepsis evaluation. We collected all serum creatinine values available within the 7 days preceding and 30 days after sepsis evaluation. Serum creatinine was obtained as part of a basic metabolic panel and was measured via an enzymatic assay (gas chromatography/isotope dilution mass spectrometry method) on a VITROS 4600 instrument (Ortho Clinical Diagnostics). Comorbid historical conditions present at the time of sepsis evaluation (chronic lung disease, NEC, intraventricular hemorrhage, congenital heart disease, and congenital surgical anomalies) were identified by *International Classification of Diseases*-9 and -10 codes in the electronic health record.

AKI Definitions

AKI was defined by nKDIGO criteria (**Table I**; available at www.jpeds.com), which have been used in large multicenter neonatal AKI studies.[7,8,20,24,25] Specifically, AKI was identified by at least a 1.5-fold increase in serum creatinine from the established baseline (the lowest value in the 7 days before a sepsis evaluation). We required that the creatinine increase to at least 0.5 mg/dL (44.2 mmol/L), in an effort to identify the most clinically significant AKI.[8,26] Severe AKI was defined as stage 2 or 3 AKI severity (at least a doubling of the baseline serum creatinine). Given challenges in extrapolating accurate daily urine output from documented urine and combination (urine and stool) data, AKI was not defined by urine output criteria. Sepsis evaluation episodes with missing baseline or postepisode creatinine values were excluded.

Statistical Analyses

Continuous data were presented as medians with IQRs, and were analyzed using Wilcoxon rank-sum tests. Categorical data were summarized as proportions, and analyzed with χ^2 or Fisher exact tests, as appropriate. To compare AKI duration between cases and controls, we used Kaplan-Meier curves and log-rank testing of equality.

We used logistic regression modeling to examine relationships between sepsis and the development of AKI, and between sepsis, AKI, and 30-day mortality. Significant variables in univariate analyses ($P < .2$), and those with clinical relevance, were considered for inclusion in multivariable models. We accounted for repeated measures with generalized estimating equations (assuming independent correlation structure) in regression analyses. Models were constructed using forward variable selection and likelihood-ratio testing. Final model fit was assessed with Hosmer-Lemeshow testing. Two-sided P values of less than .05 were considered statistically significant. All analyses were performed using the Stata statistical package (Version 16, StataCorp).

Results

Cohort Characteristics

Among 4512 sepsis evaluation episodes during the study period, 213 episodes of culture-proven sepsis (in 185 patients) were deemed cases, and were matched to 213 controls (**Figure 1**); 203 cases and 193 controls had sufficient creatinine data for inclusion in the final cohorts. No sepsis cases or matched controls required dialysis. Demographic factors were not statistically different between cohorts (**Table II**). The baseline serum creatinine was similar between groups, although cases had more serum creatinine measurements during the evaluation period (20 vs 16; $P < .001$). A higher proportion of cases had a history of NEC (32% vs 21%; $P = .02$). Sepsis cases had significantly more vasopressor days in the 7 days before and after sepsis evaluation. Seven infants in each group were cannulated for extracorporeal membrane oxygenation (ECMO). Among cases, 195 had bacteremia, 3 had fungemia, and 5 had bacterial meningitis. Lumbar punctures were performed in 76 of 203 cases (37%) compared with 8 of 193 controls (4%).

AKI Incidence and Severity

A significantly higher proportion of sepsis cases developed AKI (20%; n = 40/203) within 7 days following sepsis evaluation, compared with controls (8%; n = 16/193; $P = .001$). Although the majority of cases and controls with AKI had mild or stage 1 AKI, cases had higher AKI severity than controls ($P = .007$). Specifically, stage 2 AKI (doubling of the serum creatinine) occurred in 5.9% of cases (n = 12/203) and 2.6% of controls (n = 5/193), and stage 3 AKI (tripling of the serum creatinine) occurred in 5.4% of cases (n = 11/203) and 1.0% of controls (n = 2/193) (**Table III**).

To assess the impact of preexisting renal dysfunction (using baseline serum creatinine) on the risk of AKI, we examined 2 groups: infants with a baseline serum creatinine of 0.5 or less and greater than 0.5 mg/dL. Among infants with a baseline serum creatinine of 0.5 mg/dL or less, a significantly higher proportion of sepsis cases developed AKI (18%; n = 35/192), compared with controls (5%; n = 9/176; $P < .001$). Only 11 cases and 17 controls had a baseline serum creatinine of more than 0.5 mg/dL. In this subgroup with a higher baseline creatinine, the difference in AKI between cases (45%; n = 5/11) and controls (41%; n = 7/17) was not statistically significant ($P = 1.00$).

Among sepsis cases, there was no significant association between AKI development and type of organism ($P = .72$); 37% of cases with gram-positive infections developed AKI, compared with 31% of cases with gram-negative infections (**Tables IV** and **V**; available at www.jpeds.com). The duration of vancomycin exposure did not differ among sepsis cases with AKI (median, 2 days; IQR, 2-5 days) and sepsis cases without AKI (median, 2 days; IQR, 2-7 days), respectively ($P = .47$). We also assessed for any administration of known nephrotoxic agents within 48 hours before the sepsis evaluation (or within 7 days, in the case of intravenous contrast).[27] Although sepsis cases had higher nephrotoxic agent exposure than controls (28/203 vs 13/193; $P = .02$), there was no association between receipt of nephrotoxic agents and AKI among sepsis cases ($P = .81$) or controls ($P = .08$).

AKI Timing and Duration

The timing of AKI onset and peak severity are shown in **Figure 2**. Most AKI episodes were detected within the first 2 days after sepsis evaluation in both cases (88%; n = 35/40) and controls (75%; n = 12/16). The timing of peak AKI severity followed a similar pattern, with 73% of cases (n = 29/40) and 63% of controls (n = 10/16) reaching peak severity within the first 2 days after sepsis evaluation. There were no statistical differences in the day of AKI onset or peak severity.

AKI episode duration did not differ between cases and controls (median, 2.5 days vs 3.5 days, respectively; $P = .40$; **Table III**). Of infants with AKI, 9 of 40 sepsis cases (23%) did not return to their serum creatinine baseline within 30 days after sepsis evaluation, compared with 2 of 16 controls (13%; $P = .74$ by log-rank test; **Figure 3** [available at www.jpeds.com]). Among 9 cases who failed to return to their creatinine baseline, 8 had severe AKI and all 9 died (7 within 7 days after sepsis evaluation). Of the 2 controls who did not return to baseline, 1 had stage 2 AKI and died 1 day after sepsis evaluation, and the other had stage 1 AKI and died 4 days after sepsis evaluation. All of these patients had at least one serum creatinine obtained daily until death.

Risk Factors for AKI

Several covariates were significantly associated with development of AKI (**Table VI**). Each 0.1 mg/dL increase in the baseline serum creatinine increased the odds of developing

Table II. Cohort demographics

Characteristics	Cases n = 203	Controls n = 193	*P* value
Gestational age (weeks)	$30^{0/7}$ ($25^{0/7}$-$36^{0/7}$)	$30^{0/7}$ ($25^{0/7}$-$36^{0/7}$)	.79*
Corrected gestational age (weeks)	$40^{0/7}$ ($35^{1/7}$-$46^{1/7}$)	39 6/7 (33 4/7-$46^{0/7}$)	.77*
Day of life at time of sepsis evaluation	45 (20-114)	43 (19-109)	.67*
Male sex	114 (56)	115 (60)	.54†
Birth weight (kg)	1.22 (0.65-2.55)	1.28 (0.74-2.70)	.22*
Race			
White	77 (38)	99 (47)	.37†
Black	52 (26)	46 (24)	
Asian	3 (1)	2 (1)	
American Indian	2 (1)	0 (0)	
Two or more	8 (4)	8 (4)	
Unknown	64 (30)	46 (24)	
Comorbid conditions present at sepsis evaluation			
History of NEC	65 (32)	41 (21)	.02†
Chronic lung disease	68 (36)	71 (32)	.53†
Cardiac disease‡	28 (14)	29 (15)	.78†
Surgical conditions§	62 (31)	63 (33)	.67†
Intraventricular hemorrhage	39 (19)	33 (17)	.90†
nKDIGO baseline sCr (mg/dL)	0.30 (0.20-0.40)	0.30 (0.20-0.40)	.60*
No. of sCr values obtained per sepsis episode	20 (14-29)	16 (11-23)	<.001*
No. of sCr values obtained in the 7 days before the sepsis evaluation	6 (5-9)	6 (5-8)	.08*
No. of sCr values obtained in the 7 days post sepsis evaluation	5 (3-8)	3 (2-5)	<.001*
No. of sCr values obtained in the 30 days post sepsis evaluation	14 (8-20)	10 (5-15)	<.001*
On ECMO at time of sepsis evaluation	7 (3)	7 (4)	1.00†
Ventilator days, in the 7 days before and after sepsis evaluation	13 (1-14)	9 (2-14)	.23*
Vasopressor days, in the 7 days before and after sepsis evaluation	0 (0-14)	0 (0-14)	.06*
Mortality (overall)	57 (28)	22 (11)	<.001†
Mortality (within 30 days of sepsis evaluation)	21 (10)	8 (4)	.02†

SCr, serum creatinine.
Values are median (IQR) or number (%).
*Wilcoxon rank-sum test.
†Pearson χ^2 test.
‡Defined as congenital structural cardiac malformations present since birth (includes patent ductus arteriosus).
§Includes congenital diaphragmatic hernia, tracheoesophageal fistula, gastroschisis, omphalocele, Hirschsprung disease, intestinal atresias, myelomeningocele, and sacrococcygeal teratoma.

AKI (aOR, 1.3; 95% CI, 1.1-1.5; P = .001). Increasing vasopressor days, a history of NEC, and ECMO requirement at the time of sepsis evaluation were also significantly associated with AKI. Nephrotoxic agent administration before the sepsis evaluation was not associated with AKI in this model, and not included in the final model.

After adjustment for potential confounders, sepsis remained an independent predictor of AKI (aOR, 3.0; 95% CI, 1.5-6.2; P = .002) (Table VI). Sepsis was also associated with increased odds of severe AKI (at least stage 2 AKI) (aOR, 3.2; 95% CI, 1.3-8.2; P = .01). Vasopressor days, NEC, and ECMO remained significant covariates, but increasing ventilator days also emerged as a predictor of

Table III. AKI incidence and severity among cases and controls

Variables	Case (n = 203)	Control (n = 193)	*P* value
AKI present within 7 days of sepsis evaluation	20 (40)	8 (16)	.001*
Maximum AKI severity within 7 days			.007*
Stage 0 (No AKI)	80.3 (163)	91.7 (177)	
Stage 1 (≥1.5× serum creatinine increase from baseline)	8.4 (17)	4.7 (9)	
Stage 2 (≥2-2.9× serum creatinine increase from baseline)	5.9 (12)	2.6 (5)	
Stage 3 (≥3× serum creatinine increase from baseline)	5.4 (11)	1.0 (2)	
Peak serum creatinine within 7 days of sepsis evaluation among all patients (mg/dL)	0.30 (0.20-0.50)	0.30 (0.20-0.40)	.10†
Peak serum creatinine within 7 days of sepsis evaluation among patients who developed AKI (mg/dL)	0.70 (0.5-1.05)	1.05 (0.5-1.5)	.28†
Day of serum creatinine return to baseline,‡ among patients with AKI	3.5 (1-9.5)	5 (2.5-8.5)	.47†
Duration of AKI episode (days), among patients with AKI	2.5 (1-6)	3.5 (2-5.5)	.40†
Patients with AKI not returning to serum creatinine baseline within 30 days after sepsis evaluation	20 (8/40)	12.5 (2/16)	.71*

Values are percent (n) or median (IQR).
*Fisher exact test.
†Wilcoxon rank-sum test.
‡Day of serum creatinine return to baseline, relative to day of sepsis evaluation (day 0).

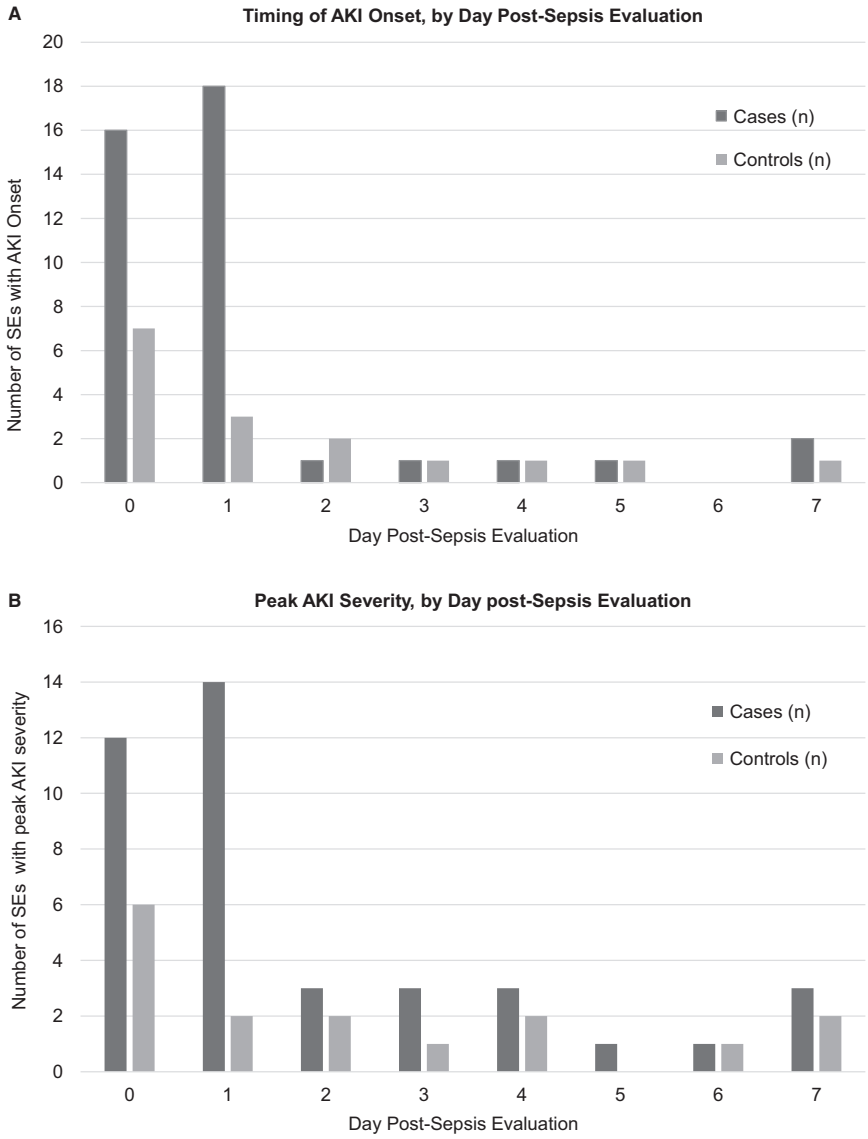

Figure 2. Timing of AKI onset and peak severity. **A,** Distribution of timing of AKI onset after sepsis evaluation, where day 0 refers to the day of sepsis evaluation. Results displayed as total number of sepsis episodes per group who developed new AKI on each day (cases n = 40, controls n = 16). **B,** Distribution of timing of peak AKI severity among cases and controls with AKI, where day 0 refers to the day of sepsis evaluation. Results displayed as total number of sepsis episodes per group who reached peak AKI severity on each day (cases n = 40, controls n = 16).

severe AKI (aOR, 1.1; 95% CI, 1.0-1.3; $P = .03$) (**Table VII**; available at www.jpeds.com). To further assess this relationship, we performed analyses with ventilator days limited to the period encompassing 3 days before and 3 days after sepsis evaluation. The impact of ventilator days on severe AKI appeared partly driven by the higher proportion of infants with severe AKI who were mechanically ventilated for the full 3 days preceding sepsis evaluation (28 of 30 infants [93%] with severe AKI, compared with 45 of 56 infants [80%] with AKI at any stage).

Because a prior episode of culture-proven sepsis could confound the odds of developing AKI in a subsequent sepsis episode, we performed a secondary analysis (in addition to the use of generalized estimating equations in the primary analysis) that excluded all episodes of recurrent sepsis from the sepsis case cohort. Multivariable regressions with this smaller sepsis case cohort (n = 177 sepsis episodes from 177 patients) yielded similar results, with sepsis significantly increasing the odds of both AKI (aOR, 3.34; 95% CI, 1.6-6.9; $P = .001$) and severe AKI (aOR, 3.52; 95% CI, 1.4-9.1; $P = .009$).

Sepsis, AKI, and 30-Day Mortality

Sepsis cases had a significantly higher 30-day mortality (10%, n = 21/203) than controls (4%, n = 8/193; $P = .003$). The overall mortality at the last follow-up was also higher among sepsis cases (29%; n = 57/203) than controls (11%; n = 22/193; $P < .001$) (**Table II**).

Table VI. Univariate and multivariate logistic regressions for development of AKI after sepsis evaluation

	Univariate analysis*			Multivariate analysis		
Variables	Unadjusted OR	95% CI	*P* value	aOR	95% CI	*P* value
Sepsis	2.71	1.46-5.03	.002	3.02	1.48-6.16	.002
Baseline serum creatinine†	1.32	1.13-1.52	<.001	1.30	1.11-1.52	.001
Gestational age (weeks)	0.95	0.89-0.998	.04	0.93	0.85-1.02	.14
Corrected gestational age (weeks)	0.97	0.94-1.00	.08	1.00	0.96-1.04	.99
Ventilator days in the 7 days before and after sepsis evaluation	1.11	1.04-1.17	.001	1.04	0.97-1.12	.30
Vasopressor days in the 7 days before and after sepsis evaluation	1.20	1.10-1.30	<.001	1.18	1.06-1.32	.003
ECMO requirement at time of sepsis evaluation	3.61	1.16-11.2	.03	7.92	1.84-34.09	.005
History of NEC	2.16	1.20-3.88	.01	2.25	1.09-4.66	.03
Chronic lung disease	0.94	0.52-1.71	.84	0.88	0.37-2.09	.78
Congenital heart disease	1.56	0.75-3.24	.23	2.45	1.01-5.97	.05
Congenital surgical conditions	0.62	0.32-1.19	.15	0.44	0.16-1.22	.11
Intraventricular hemorrhage	0.97	0.47-2.04	.95	0.54	0.22-1.31	.17

*Univariate and multivariate analysis presented only for variables included in the final multivariable model. Infant sex and race were also tested on univariate analysis, and were not associated with AKI development, thus not included in the final model.
†Serum creatinine base unit 0.1 mg/dL.

In the multivariable logistic regression model, AKI development within 7 days of sepsis evaluation was significantly associated with 30-day mortality (aOR, 4.5; 95% CI, 1.3-15.6; $P = .02$; **Table VIII** [available at www.jpeds.com]). Sepsis was also associated with an increased odds of 30-day mortality (aOR, 2.3; 95% CI, 0.7-8.0), although this difference was not statistically significant ($P = .18$). To examine the impact of concurrent sepsis and AKI on mortality, we evaluated a sepsis-AKI interaction term; however, it was not statistically significant and not included in the final model. The elimination of recurrent sepsis episodes from the sepsis case cohort did not alter the associations of sepsis and AKI with 30-day mortality.

A secondary regression model evaluating the impact of severe AKI on 30-day mortality yielded similar results; severe AKI had an even greater association with mortality (aOR, 5.6; 95% CI, 2.0-15.9; $P = .001$; **Table IX** [available at www.jpeds.com]). A sepsis-severe AKI interaction term remained statistically nonsignificant.

Discussion

In this study, we quantified the incidence, severity, and natural history of AKI in late-onset neonatal sepsis. We observed that infants with late-onset sepsis are at significant risk for renal dysfunction within 7 days after sepsis evaluation, with a 3-fold increased odds of developing AKI. These results expand upon the only other published study of neonatal sepsis-associated AKI, which similarly reported a 26% incidence of sepsis-associated renal dysfunction.[28] However, that study had important differences: most sepsis episodes were early onset (occurring <72 hours of life), only 20% of infants had positive blood cultures, and renal dysfunction was primarily defined by elevated blood urea nitrogen. In contrast, our study uses more contemporary AKI criteria, and a stricter definition of culture-proven sepsis, strengthening the validity of our findings and the potential for replicability.

Increasing adoption in neonatal AKI research provides opportunities for evaluation and refinement of the nKDIGO AKI criteria. We applied the nKDIGO criteria with a conservative modification requiring the serum creatinine to increase to at least 0.5 mg/dL, in an effort to identify AKI owing to significant creatinine elevations.[8,26] The inclusion of episodes with AKI defined by small creatinine fluctuations (eg, from 0.2 to 0.3 mg/dL) may have otherwise obscured the association between sepsis and clinically significant AKI. We suggest that future neonatal AKI studies consider measuring the performance of this nKDIGO criteria modification in other clinical contexts.

Sepsis-associated AKI is a unique AKI phenotype described in humans and animal models that appears to be driven by infection-mediated renal hypoperfusion with resultant ischemic-reperfusion injury, as well as cytokine- and oxidant-mediated direct renal injury (particularly via renal tubular apoptosis and microthrombotic insults).[29] In adults, sepsis-associated AKI is associated with worsened illness severity (higher requirements for vasopressors, mechanical ventilation, and fluid resuscitation) and increased episode-level mortality, compared with critically ill patients with nonseptic AKI.[30] In contrast, the AKI pathophysiology experienced by the uninfected control infants in this study was less likely to have been inflammatory in nature and may be attributable to other etiologies, including relative renal hypoperfusion from fluid shifts, hypotension, or medication effects.

Substantial AKI rates among cases and controls underscore the role of critical illness in predisposing to renal dysfunction. Despite not having culture-proven sepsis, control infants nonetheless had sufficient clinical instability to warrant sepsis evaluations. Clinical markers of cardiorespiratory dysfunction (need for vasopressors, mechanical ventilation, and ECMO) were independent predictors of severe AKI, consistent with prior reports.[31,32] Existing renal dysfunction may also predispose to new AKI; we found that increasing baseline serum creatinine predicted AKI development, and among all

infants with baseline creatinine of greater than 0.5 mg/dL, 43% developed AKI after sepsis evaluation.

Nephrotoxic medications are frequently cited as AKI risk factors.[33] Antimicrobial medications used for the treatment of suspected or confirmed neonatal infections (eg, vancomycin and gentamicin) are among the most commonly prescribed in NICUs, and their potential additive impact on short- and long-term renal dysfunction, especially in the setting of other factors implicated in renal injury, warrants caution.[34] There were relatively low rates of nephrotoxic agent exposure preceding sepsis evaluation in this study, which were not associated with AKI development among infants with sepsis. In our study, the majority of all AKI developed within the first 2 days after sepsis evaluation, during which time both cases and controls would have received vancomycin. Although vancomycin exposure could have contributed to AKI, it does not fully explain the higher AKI rates in sepsis cases. In addition, we acknowledge that intravascular volume depletion from furosemide may also cause nephrotoxicity.

The prevalence of AKI is likely underappreciated; surveys suggest that clinicians lack familiarity with evolving neonatal AKI criteria and AKI's role in predisposing to chronic kidney disease.[35,36] More frequent serum creatinine monitoring has been associated with higher AKI diagnosis rates, and less frequent monitoring associated with higher AKI-associated mortality.[9] In our study, case infants had significantly more measured creatinine values than controls in the 7 and 30 days after sepsis evaluation. This result could have contributed to higher AKI detection in infants with sepsis, but could also reflect clinical decision-making for enhanced surveillance in the setting of culture-proven infection or clinical deterioration.

Even small increases in serum creatinine can increase the risk of chronic kidney disease in vulnerable premature infants.[37,38] Although the majority of AKI associated with sepsis evaluations was short lived and mild in our study, 11% of cases and 3.5% of controls experienced severe AKI. Failure of return to baseline creatinine within 30 days was highly correlated with mortality, emphasizing the importance of close renal function monitoring after episodes of clinical deterioration.

AKI and sepsis both independently increased the odds of mortality within 30 days after sepsis evaluation. We could not fully assess the impact of sepsis-associated AKI on mortality, owing to insufficient power. However, a large retrospective analysis of pediatric intensive care unit patients showed that sepsis-associated AKI was an independent predictor of death or moderate functional disability (aOR, 2.5; 95% CI, 1.5-4.2; $P = .001$).[39] Further study in larger, multicenter cohorts is needed to assess the relationship between sepsis-associated AKI and mortality in the NICU.

This study is enhanced by the inclusion of a matched control group of infants undergoing (ultimately negative) sepsis evaluations. Our use of rigorous definitions for late-onset sepsis and AKI minimizes the risk of misclassification bias. The availability of a robust, electronic health record-linked sepsis registry allowed for targeted data extraction and highly granular analyses of creatinine trends for a 38-day period surrounding each sepsis evaluation. This analysis was further strengthened by adjustment for common comorbid conditions of prematurity and surrogates for cardiorespiratory dysfunction, which could otherwise confound analysis of the sepsis-AKI relationship.

Our study had several limitations. This was a single-center study conducted in a quaternary NICU, and these results may not be generalizable to all NICUs given the case mix and level of complexity of our sample population. Although a matched study afforded the opportunity to study AKI in infants with and without culture-proven sepsis, the control group may have inherent risk factors for AKI that could have underestimated the differences between the groups. Despite analyzing almost 400 sepsis evaluations, we lacked the power to fully assess the complex relationship between sepsis, AKI, and mortality. There was a risk for ascertainment bias in infants who had serum creatinine data sampled at varying frequencies. Owing to the limitations in reliably estimating urine volumes from urine and combination output data, we were unable to define AKI by urine output criteria.

In this study, we identified that infants with culture-proven sepsis had an increased risk for AKI and increased AKI severity, compared with control infants with negative sepsis evaluations. These results highlight the need for AKI surveillance in critically ill patients in the NICU, specifically in infants with sepsis who are at risk for renal dysfunction. We suggest that infants with suspected sepsis, particularly those with laboratory-confirmed infections, should undergo routine monitoring for AKI in the 48 hours to 7 days after sepsis evaluation. Further study in larger cohorts is needed to assess the impact of sepsis-associated AKI on later development of chronic kidney disease and mortality. ■

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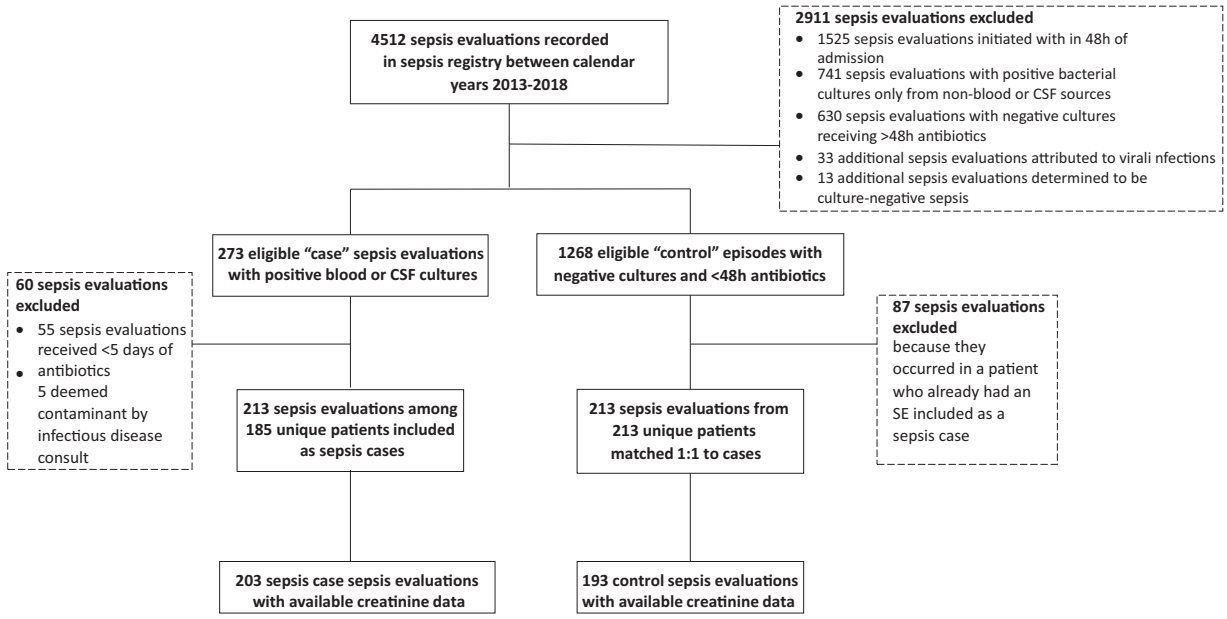

Figure 1. Flow diagram of cohort selection. There were 213 episodes of culture-proven late-onset sepsis that met the inclusion criteria and were matched by gestational age and corrected gestational age to 213 control patients who underwent negative sepsis evaluations. The final cohorts (after excluding participants with insufficient creatinine data to make AKI determinations) included 203 cases and 193 controls.

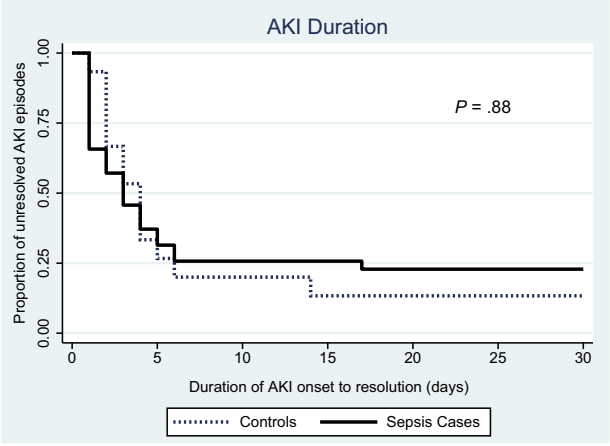

Figure 3. AKI duration. Kaplan-Meier curve displaying AKI duration among cases (n = 40) and controls (n = 16). Five case episodes and 1 control episode had AKI resolution on the day of sepsis evaluation (day 0). There were 9 case episodes and 2 control episodes that failed to return to baseline serum creatinine by 30 days postsepsis evaluation, all of whom died.

Table I. The nKDIGO criteria

AKI stages	Serum creatinine (SCr)*,†	Urine output
0	No change in SCr or rise <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h OR SCr rise ≥ 1.5-1.9× baseline SCr	<0.5 mL/kg/h for 6-12 hours
2	SCr rise ≥ 2.0-2.9× baseline SCr	<0.5 mL/kg/h for >12 hours
3	SCr rise ≥ 3× baseline SCr OR SCr ≥ 2.5 mg/dL OR Need for renal replacement therapy	<0.3 mL/kg/h for >24 hours OR Anuria for >12 hours

SCr, serum creatinine.
Criteria as proposed by Jetton et al.[7] Content reproduced with permission of the publisher.
*To convert to SI units (mmol/L), multiply the SCr in mg/dL by a conversion factor of 88.4.
†In addition to meeting fold-change increase requirements, we additionally required that the serum creatinine rise to at least 0.5 mg/dL to qualify as AKI.

Table IV. Organism distribution in sepsis cases by nKDIGO AKI status

Organisms	No. of sepsis episodes attributed to pathogen*	No AKI	Stage 1	Stage 2	Stage 3
Bacillus sp	2	2 (100)	0 (0)	0 (0)	0 (0)
Group B *Streptococcus*/*Streptococcus agalactiae*	6	3 (50)	3 (50)	0 (0)	0 (0)
Candida sp	3	2 (67)	0 (0)	1 (33)	0 (0)
Citrobacter	1	1 (100)	0 (0)	0 (0)	0 (0)
Coagulase-negative *Staphylococcus* sp	61	44 (72)	11 (18)	5 (8)	0 (0)
Enterobacter	12	9 (75)	2 (17)	0 (0)	1 (8)
Enterococcus sp	18	10 (56)	3 (17)	3 (17)	2 (11)
Escherichia sp	23	18 (78)	1 (4)	3 (13)	1 (4)
Haemophilus	1	1 (100)	0 (0)	0 (0)	0 (0)
Klebsiella sp	17	10 (59)	4 (24)	1 (6)	2 (12)
Kocuria/*Micrococcus*	1	1 (100)	0 (0)	0 (0)	0 (0)
Methicillin-sensitive *Staphylococcus aureus*	43	29 (67)	26 (9)	2 (5)	1 (2)
Methicillin-resistant *Staphylococcus aureus*	7	3 (43)	2 (29)	1 (14)	2 (14)
Pseudomonas	9	5 (56)	0 (0)	2 (22)	3 (33)
Ralstonia sp	1	1 (100)	0 (0)	0 (0)	0 (0)
Serratia	3	3 (100)	0 (0)	0 (0)	0 (0)
Stenotrophomonas spp.	1	1 (100)	0 (0)	0 (0)	0 (0)
Proteus spp.	1	1 (100)	0 (0)	0 (0)	0 (0)
Viridans *Streptococcus* (*mitis/oralis/parasanguinis*)	5	5 (100)	0 (0)	0 (0)	0 (0)

Values are number (%) unless otherwise indicated.
*The total number of sepsis episodes was 203, but 9 sepsis episodes had polymicrobial growth of initial blood cultures; therefore, the total pathogen count equals 215. Seven episodes had growth of 2 pathogens, one episode had growth of 3 pathogens, and one episode had growth of 4 pathogens.

Table V. AKI Presence in sepsis cases by organism class

Organism types	AKI present	No AKI present	Total*
Gram positive	30 (37)	52 (63)	82
Gram negative	20 (31)	45 (69)	65
Coagulase-negative *Staphylococcus*	17 (28)	44 (72)	61
Fungi	1 (33)	2 (67)	3

Values are number (%).
*This total (211) reflects the polymicrobial nature of some blood cultures and exceeds the 203 sepsis evaluations included in analysis.

Table VII. Univariate and multivariate logistic regressions for development of severe AKI after sepsis evaluation

	Univariate analysis*			Multivariate analysis		
Variables	Unadjusted OR	95% CI	*P* value	aOR	95% CI	*P* value
Sepsis	3.4	1.4-8.1	.006	3.2	1.3-8.2	.01
Baseline serum creatinine†	1.1	0.97-1.2	.17	2.6	1.0-6.8	.05
Gestational age (weeks)	0.9	0.9-1.0	.03	0.9	0.8-1.0	.13
Corrected gestational age (weeks)	1.0	0.96-1.03	.99	1.0	1.0-1.1	.37
Ventilator days in the 7 days before and after sepsis evaluation	1.2	1.1-1.3	.001	1.1	1.0-1.3	.03
Vasopressor days in the 7 days before and after sepsis evaluation	1.2	1.1-1.3	.001	1.2	1.0-1.3	.03
ECMO at time of sepsis evaluation	3.6	0.9-13.6	.06	5.6	1.0-30.5	.05
NEC	2.6	1.2-5.5	.01	2.2	0.9-5.4	.08
Chronic lung disease	1.7	0.8-3.6	.171	1.1	0.4-3.3	.86
Congenital heart disease	1.5	0.6-4.0	.366	2.4	0.8-7.4	.12
Congenital surgical conditions	0.6	0.3-1.5	.32	0.7	0.2-2.8	.66
Intraventricular hemorrhage	1.4	0.6-3.4	.45	0.7	0.2-1.9	.48

*Univariate and multivariate analysis presented only for variables included in the final multivariable model. Infant sex and race were also tested on univariate analysis, and were not significantly associated with AKI development, thus not included in the final model.
†SCr, base unit 0.1 mg/dL.

Table VIII. Univariate and multivariate logistic regressions for development of 30-day mortality after sepsis evaluation

	Univariate analysis*			Multivariate analysis		
Variables	**Unadjusted OR**	**95% CI**	***P* value**	**aOR**	**95% CI**	***P* value**
AKI	3.25	1.42-7.42	.005	4.51	1.31-15.55	.02
Sepsis	10.06	4.5-22.5	<.001	2.33	0.68-8.04	.18
Baseline serum creatinine†	1.06	0.97-1.15	.18	1.02	0.86-1.20	.82
Gestational age (weeks)	0.98	0.92-1.05	.58	1.03	0.88-1.22	.70
Corrected gestational age (weeks)	0.98	0.94-1.02	.36	1.01	0.95-1.08	.73
Ventilator days in the 30 days after a sepsis evaluation	1.06	0.94-0.99	<.001	0.99	0.94-1.05	.82
Vasopressor days in 30 days after a sepsis evaluation	1.17	1.02-1.10	<.001	1.20	1.12-1.28	<.001
ECMO at time of sepsis evaluation	5.49	1.62-18.61	.006	10.1	0.88-115.91	.05
NEC	0.94	0.41-2.16	.89	0.64	0.17-2.44	.51
Chronic lung disease	1.18	0.56-2.48	.67	2.19	0.46-10.4	.32
Congenital heart disease	1.14	0.42-3.09	.80	0.92	0.19-4.37	.92
Congenital surgical conditions	0.31	0.11-0.91	.03	0.04	0.00-0.59	.02
Intraventricular hemorrhage	1.01	0.40-2.55	.98	0.72	0.15-3.47	.68

*Univariate and multivariate analysis presented only for variables included in the final multivariable model. Infant sex and race were also tested on univariate analysis, and were not significantly associated with mortality, thus not included in the final model.
†SCr, base unit 0.1 mg/dL.

Table IX. Univariate and multivariate logistic regressions for development of 30-day mortality following sepsis evaluation, with severe AKI

	Univariate analysis*			Multivariate analysis		
r	**Unadjusted OR**	**95% CI**	***P* value**	**aOR**	**95% CI**	***P* value**
Severe AKI†	9.1	3.8-22.2	<.001	5.6	2.0-15.9	.001
Sepsis	10.06	4.5-22.5	<.001	2.5	0.9-6.7	.07
Baseline serum creatinine‡	1.06	0.97-1.15	.18	1.9	0.7-5.7	.22
Gestational age (weeks)	0.98	0.92-1.05	.58	1.1	1.0-1.2	.17
Corrected gestational age (weeks)	0.98	0.94-1.02	.36	1.0	0.9-1.0	.78
Ventilator days in the 30 days after sepsis evaluation	1.06	0.94-0.99	<.001	1.0	0.9-1.1	.57
Vasopressor days in 30 days after sepsis evaluation	1.17	1.02-1.10	<.001	1.3	1.1-1.4	.001
ECMO at time of sepsis evaluation	5.49	1.62-18.61	.006	19.3	2.8-132.8	.003
NEC	0.94	0.41-2.16	.89	0.7	0.2-2.0	.51
Chronic lung disease	1.18	0.56-2.48	.67	1.7	0.5-5.8	.39
Congenital heart disease	1.14	0.42-3.09	.80	0.8	0.2-2.9	.73
Congenital surgical conditions	0.31	0.11-0.91	.03	0.04	0.004-0.300	.001
Intraventricular hemorrhage	1.01	0.40-2.55	.98	1.1	0.4-3.7	.82

*Univariate and multivariate analysis presented only for variables included in the final multivariable model. Infant sex and race were also tested on univariate analysis, and were not significantly associated with mortality and thus were not included in the final model.
†Severe AKI defined as stage 2 or 3 AKI.
‡SCr, base unit 0.1 mg/dL.